# Lumateperone (Caplyta®) New Drug Update

**January 2020**

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| **Nonproprietary Name** | lumateperone |
| **Brand Name** | Caplyta |
| **Manufacturer** | Intra-Cellular Therapies |
| **Form** | Capsule |
| **Strength** | 42 mg |
| **FDA Approval** | December 20, 2019 |
| **Market Availability** | Available |
| **FDA Approval Classification** | Standard Review |
| **FDB Classification- Specific Therapeutic Class (HIC3)** | Antipsychotic, Atypical, Dopamine, Serotonin Antagonist (H7T) |

## INDICATION[1]

Lumateperone (Caplyta) is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.

The exact mechanism of action of lumateperone in schizophrenia is unknown but it is thought to provide selective and simultaneous modulation of serotonin, dopamine, and glutamate.

## PHARMACOKINETICS

Once daily administration of lumateperone will lead to steady state in approximately 5 days, with increases in exposure proportional to the dose. The maximum concentration ($C_{max}$) of lumateperone is reached approximately 1 to 2 hours after the dose. Administration with food will delay the time to maximum concentration ($T_{max}$) by approximately 1 hour, and a high fat meal would result in a decrease in $C_{max}$ of approximately 33%. Lumateperone is 97.4% protein bound. Lumateperone is extensively metabolized to over 20 metabolites with various enzymes involved, including uridine 5'-diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR) 1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2. The terminal half-life is approximately 18 hours after intravenous administration. A human mass-balance study demonstrated <1% of the radioactive dose was excreted as unchanged in the urine, with 58% and 29% recovered in the urine and feces, respectively.

## CONTRAINDICATIONS/WARNINGS

Contraindications for lumateperone include known hypersensitivity to the active ingredient or any of the components.

Lumateperone has a boxed warning related to increased mortality in elderly patients with dementia-related psychosis. Other warnings include increased incidence of cerebrovascular adverse reactions in elderly patients with dementia-related psychosis (e.g., stroke, transient ischemic attack), neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain), decrease in white blood cells (e.g., leukopenia, neutropenia, agranulocytosis), orthostatic hypotension/syncope, falls, dysphagia, body temperature dysregulation, seizures, and potential cognitive and motor impairment.

## DRUG INTERACTIONS

Lumateperone should be avoided with concomitant CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, efavirenz, etravirine, modafinil, armodafinil, pioglitazone, prednisone) due to a decreased exposure to the drug. Lumateperone should be avoided with UGT inhibitors (e.g., valproic acid, probenecid) and moderate or strong CYP3A4 inhibitors (e.g., amprenavir, ciprofloxacin, cyclosporine, diltiazem, fluvoxamine, verapamil) due to an increased exposure to the drug leading to an increased risk of adverse reactions.

## COMMON ADVERSE EFFECTS

The most common adverse reactions in clinical trials that occurred in patients who received short term therapy from 4 to 6 weeks at an incidence ≥ 2% (reported as incidence versus placebo, respectively) included somnolence/sedation (24% versus 10%), nausea (9% versus 5%), dry mouth (6% versus 2%), dizziness (5% versus 3%), increase in creatine phosphokinase (4% versus 1%), fatigue (3% versus 1%), vomiting (3% versus 2%), increase in hepatic transaminases (2% versus 1%), and decreased appetite (2% versus 1%).

## SPECIAL POPULATIONS

### Pregnancy

Available data from case reports on lumateperone use in pregnant women are insufficient to establish any drug associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes.

### Pediatrics

Safety and effectiveness of lumateperone have not been established in pediatric patients.

### Geriatrics

Clinical studies with lumateperone did not include any patients aged ≥ 65 years to determine whether they respond differently than younger patients. Lumateperone is not approved for the treatment of patients with dementia-related psychosis as antipsychotic drugs increase the risk of death in elderly patients with this condition.

### Hepatic Impairment

Lumateperone is not recommended in patients with moderate (Child-Pugh class B) to severe hepatic impairment (Child-Pugh class C) due to increased exposure to the drug. There is no recommended dosage adjustment for patients with mild hepatic impairment (Child-Pugh class A).

## Renal Impairment

There are no dosage adjustment recommendations for patients with renal failure.

## DOSAGES

The recommended dosage is 42 mg administered orally once daily with food. Dose titration is not required.

## CLINICAL TRIALS[2,3,4]

*A literature search was performed using "lumateperone" and "schizophrenia."*

Study 1 (NCT01499563; phase 2) and Study 2 (NCT02282761; phase 3) were 4-week, randomized, double-blind, placebo-controlled, multicenter studies evaluating the efficacy of lumateperone. Both trials included patients with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual (DSM) IV-TR or DSM-5 criteria, respectively. The primary measure in both studies was the Positive and Negative Syndrome Scale (PANSS) total score, a 30-item, clinician-rated scale used to measure the symptoms of schizophrenia. Each item is scored from 1 (absence of symptoms) to 7 (extremely severe symptoms) for a total score ranging from 30 to 210 reflecting overall disease severity.

Study 1 included a total of 335 patients who were randomized to receive either lumateperone 42 mg, lumateperone 84 mg, risperidone 4 mg, or placebo. Study 2 included 450 patients who were randomized to receive either lumateperone 28 mg, lumateperone 42 mg, or placebo. Patients randomized to lumateperone 42 mg showed a statistically significant reduction from baseline to day 28 in the PANSS total score compared to placebo, with a placebo-subtracted difference in least-squares mean difference (LSMD) from baseline of -5.8 (95% confidence interval [CI], -10.5 to -1.1; p=0.017) in Study 1 and -4.2 in Study 2 (95% CI, -7.8 to -0.6; p=0.02). The treatment effect in the lumateperone 28 mg and 84 mg groups, however, did not demonstrate a statistically significant reduction from baseline to day 28 in the PANSS total score when compared to placebo. In Study 1, the placebo-subtracted difference in LSMD from baseline was similar between the lumateperone 42 mg and the risperidone 4 mg groups.

## OTHER DRUGS USED FOR CONDITION[5]

The first- and second-generation antipsychotics are the treatment of choice for schizophrenia. The first-generation antipsychotics used for the treatment of schizophrenia include chlorpromazine, fluphenazine, haloperidol (generic, Haldol®, Haldol® Decanoate), loxapine (generic, Adasuve®), molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine. The second-generation antipsychotics used for the treatment of schizophrenia include aripiprazole (Abilify®, Abilify Discmelt®, Abilify Maintena®, Abilify Mycite®, Aristada™), asenapine (Saphris®, Secuado®), brexpiprazole (Rexulti®), cariprazine (Vraylar®), clozapine (Clozaril®, Fazaclo®, Versacloz®), iloperidone (Fanapt®), lurasidone (Latuda®), olanzapine (Zyprexa™, Zyprexa® Relprevv™, Zyprexa® Zydis®), paliperidone (Invega®, Invega® Sustenna™, Invega Trinza®), quetiapine (Seroquel®, Seroquel XR®), risperidone (Perseris™, Risperdal®, Risperdal Consta®, Risperdal® M-tab™), and ziprasidone (Geodon®).

## PLACE IN THERAPY[6,7]

The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia does not contain an evidence-based ranking of the first- and second-generation antipsychotics or an algorithmic approach to antipsychotic selection due to limitations in the available

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clinical trial data (e.g., limited head-to-head studies, significant heterogeneity in clinical trial design, and limited data for multiple antipsychotic medications). Furthermore, the guidance does not include a preference for 1 agent over another due to interpatient variability in symptoms and response to medications which can be expected. Although the mechanism of action of lumateperone is currently unknown, the efficacy could be mediated by antagonistic activity at central serotonin 5-HT$_{2A}$ receptors and postsynaptic antagonist activity at central dopamine D$_2$ receptors. Prescribers involved in the treatment of schizophrenia must navigate many patient-specific and drug-related factors that have to be synthesized in order to determine a patient's treatment plan. Patients with schizophrenia may require multiple changes in therapy due to limited response or the occurrence of unwanted side effects. Lumateperone offers clinicians another treatment option FDA-approved for schizophrenia that employs a potentially unique mechanism as a first-in-class antipsychotic that acts synergistically through the serotonin, dopamine, and glutamate systems.

## SUGGESTED UTILIZATION MANAGEMENT

| Anticipated Therapeutic Class Review (TCR) Placement | Antipsychotics |
|---|---|
| Clinical Edit | **Initial Approval Criteria**<br>▪ Patient must be ≥ 18 years of age; **AND**<br>▪ Patient must have a diagnosis of schizophrenia based upon DSM-5 criteria; **AND**<br>▪ Lumateperone is NOT being used for dementia-related psychosis; **AND**<br>▪ Patient does NOT have moderate to severe hepatic impairment (Child-Pugh classes B or C); **AND**<br>▪ Patient is NOT taking any of the following drugs with clinically relevant interactions:<br>  – Cytochrome P450 3A4 (CYP3A4) inducers (e.g., carbamazepine, phenytoin, rifampin, efavirenz, etravirine, modafinil, armodafinil, pioglitazone, prednisone); **OR**<br>  – Moderate to strong CYP3A4 inhibitors (e.g., amprenavir, ciprofloxacin, cyclosporine, diltiazem, fluvoxamine, verapamil); **OR**<br>  – UGT inhibitors (e.g., valproic acid, probenecid); **AND**<br>▪ Patient has tried and failed ≥ 2 preferred atypical antipsychotics.<br><br>**Renewal Criteria**<br>▪ Patient must continue to meet the above criteria; **AND**<br>▪ Patient must have disease improvement and/or stabilization; **AND**<br>▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., agranulocytosis, body temperature dysregulation, cognitive/motor impairment, leukopenia, metabolic changes, neuroleptic malignant syndrome, neutropenia, orthostatic hypotension/syncope, tardive dyskinesia). |
| Quantity Limit | 30 capsules/30 days |
| Duration of Approval | 12 months (initial and renewal) |
| Drug to Disease Hard Edit | Dementia-related psychosis |

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# REFERENCES

1 Caplyta [Package Insert]. Hamilton, Bermuda; Intra-Cellular Therapies; December 2019.

2 Caplyta [Package Insert]. Hamilton, Bermuda; Intra-Cellular Therapies; December 2019.

3 Lieberman JA, Davis RE, Correll CU, et al. ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. Biol Psychiatry. 2016; 79(12): 952-61. DOI: 10.1016/j.biopsych.2015.08.026. Available at: https://www.biologicalpsychiatryjournal.com/article/S0006-3223(15)00694-0/pdf. Accessed January 28, 2020.

4 Correll CU, Davis RE, Weingart M, et al. Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. JAMA Psychiatry. 2020 Jan 8. DOI: 10.1001/jamapsychiatry.2019.4379. [Epub ahead of print]. Available at: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2758022. Accessed January 28, 2020.

5 Clinical Pharmacology [database online]. Tampa, FL: Elsevier; 2020. Available at: http://www.clinicalpharmacology.com.

6 American Psychiatric Association. Treatment of Patients with Schizophrenia. Available at: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed January 24, 2020.

7 Caplyta [Package Insert]. Hamilton, Bermuda; Intra-Cellular Therapies; December 2019.